

Assessment of the Impairment in Domain functionalities and Executive Functions in Euthymic Patients, with Bipolar Disorder I/II - Utilizing the FAST and FAB tests

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Keywords— Bipolar Disorder, Euthymia, Executive Function, Frontal Assessment Battery – FAB, Functioning Assessment Short Test – FAST, Neuropsychological Assessment.

Abstract— Objective: In this article, we focus on assessing two key predictors of outcomes in Bipolar Disorder (BD): cognition and functionality performance, and researching for a correlation between them. Methods: Subjects were patients with BD in the euthymic phase ($n=50$), and healthy controls ($n=25$). Psychosocial functioning was evaluated using the Functioning Assessment Short Test (FAST), and the same group underwent the Frontal Assessment Battery (FAB) to assess the Executive Functions (EF). Clinical and sociodemographic characteristics were analyzed using one-way analysis of variance or the chi-square test. To verify a correlation between FAB and FAST tests, we used the Spearman Correlation Coefficient. Results: Patients with BD showed higher FAST total scores (24.60 ± 11.09) than healthy controls (9.80 ± 5.94) ($p < 0.001$), and patients with BD showed lower FAB total scores (13.56 ± 2.81) than healthy control (15.72 ± 1.64) ($p < 0.001$). Associated with these results, bipolar patients showed higher FAST scores in all domains predominantly with moderate impairment (score 21-40), and also lower scores in the following three domains: conceptualization, sensitivity to interference, and inhibitory control in the FAST test ($p < 0.05$). The correlation between the variables FAB and FAST presented a moderate intensity ($r^2 = -0.539$). Conclusion: This study reinforced the impact of BD in functionality and the EF, demonstrating alterations in several domains: social, occupational, and cognitive functions impairment. Understanding them is crucial for these patients, which increases the possibility of rehabilitation and the response to treatment.

I. INTRODUCTION

Bipolar Disorder (BD) is a chronic and severe disease that affects approximately 1.1% of the world population and is associated with a high rate of morbidity, mortality, suicide, and clinical comorbidities [1]. Its pathophysiology is complex, multifactorial, and is not yet fully understood, being influenced by genetic and environmental factors

[2]. Multiple changes occur in the brain, such as neuroplasticity, neurotransmission failures, apoptosis, activation in the immune-inflammatory process, and more recently, oxidative stress [3].

These events involve a pathological reorganization in the brain and therefore are associated with morphological modifications, such as the reduced volume of the

prefrontal cortex, hippocampus, and enlarged amygdala. These structural and biochemical changes are highly recurrent and disabling, developing a process known as neuroprogression. These alterations are possibly secondary to multiple episodes of mania and depression during the disease, raising the hypothesis that bipolar patients may have had changes in their neurocognitive performance with an impact on their daily functionality and psychosocial aspects [4]; [5];[6];[7];[8];[9]. These modifications are usually measurable and characterized by reductions mainly in Executive Functions (EF). The EF is a generic term to describe cognitive processes that allow a person to develop a flexible and independent goal-directed behavior [10];[11]. The EF presents particularly three main domains (working memory, inhibition, and cognitive flexibility), and they are accepted as the basis for other more complex EF, such as; planning, problem-solving, abstract reasoning, among others [12];[13];[14];[15]. Evaluating the specific EF domains, is a time-consuming and difficult task. For this reason, different neuropsychological tests i.e., California Verbal Learning Test; Rey Complex Figure Test; Trail making Test; Verbal Working Memory Test, Wisconsin Card Sorting Test, and more recently FAB Test can be used [16]. An impairment of EF is present in several neurological conditions, such as neurodegenerative disorders, traumatic brain injuries, strokes, and more recently in various psychiatric disorders like substance-use disorders [17];[18], and schizophrenia [19]. Although, the significance of EF deficits is not yet fully understood, many studies have shown that changes in their neurocognitive performance, suggest that they may negatively impact the overall functionality of patients, and be at least partially responsible for the low rate of functional recovery in bipolar patients, even during periods between episodes (euthymia) which were observed in a high proportion of patients [20].

Research has been done in both longitudinal and cross-sectional data about cognitive and psychosocial functioning in BD I/II patients, during different episodes of the disease (mania, depression, and even euthymia), demonstrating that these changes in neurocognition and psychosocial adaptation of these patients compromise their functionality [21];[22];[23];[24];[25];[26];[27];[28]. It was believed that bipolar patients had to reach a euthymic state to recover from the symptoms and their functional capacity, stabilizing the cognitive impairments, and presenting an essential improvement in psychosocial activities. This phenomenon has been questioned recently, and new evidence emerged showing that even in euthymia, some patients had difficulty recovering their premorbid functions after clinical remission, observing a limitation in

occupational activities and psychosocial integration [29];[30]. Thus, remission in BD (euthymia) is not synonymous with patients' recovery and functionality [31]. Gitlin et al. [32] have already described that despite the treatment, 73% of the patients had relapsed with depression and mania many times over a period of five years. Even for those who did not relapse, changes in their psychosocial functioning were observed, especially in the occupational area, generating a poor prognosis for the disease. The hypothesis related to this phenomenon is the cognitive deficits deriving from chronicity of the clinical course, and persistent subsyndromal symptoms [21];[31]. Also, research with patients after the first manic episode, showed that functional impairments were present in up to 70% of patients [33]. Furthermore, occupational impairment was not significantly different in patients during their first episode, than in those with multiple episodes. Even in a prospective observational study including 3681 patients with episodes of acute or mixed mania for two years (2004 to 2006), Goetz et al. [34], found that functional and occupational impairment were already present in the year before their first mania episode. This low functional performance seems to be the norm in patients with BD. However, studies are lacking to establish which clinical variables are associated with cognitive impairment, and what are the impacts of these impairments in BD [35];[36];[37]. Therefore, the objectives of this study are to determine a) if there is any impairment in functionality, and in the frontal neurocognitive functions between a group of BD I/II patients in their euthymic state, when compared to healthy controls, using the FAST and FAB Tests respectively; b) if there are any differences in the demographic, clinical, and pharmacological characteristics in a euthymic population. c) if any cognitive deficits occurred, which deficits were the most frequent in patients with BD during euthymia d) if the cognitive and functional deficits in euthymic patients are correlated with patients younger and older e) if the cognitive and functional deficits in euthymic patients are correlated with the time of study f) to research which category of cut-off scores prevailed in the FAST and the FAB tests among euthymic patients g) to correlate the variables in the FAB and FAST tests, and evaluate if the scores in the FAB (EF) presented an influence on the FAST (functionality).

II. METHOD

2.1 Ethics

This study was approved by the Research Ethics Committee of Universidade da Região de Joinville - UNIVILLE (protocol number 655.037) and followed the

ethical rules of the Helsinki Declaration of 1975. All participants provided written informed consent before entering the study. Each patient underwent a clinical and psychiatric evaluation, where demographic, anthropometric, pharmacological data and clinical variables (age at onset, disease duration, number of episodes, number of hospitalizations, time since last relapse and hospitalization, history of suicide attempts, history of psychosis symptoms, rapid cycling history, and family psychiatric history), were collected.

2.2 Participants

The study evaluated 50 outpatients, with BD types I/II, in the euthymic state, who were recruited from the Porto Seguro Psychiatric Hospital, located in the city of Curitiba, Brazil. All 50 patients were compared against 25 healthy controls. The groups were matched by age, gender, and educational level. The participants were divided into two groups, one group with 50 euthymic BD patients and 25 healthy controls. Most bipolar patients (84%) of this study participated in a psychoeducation program, implemented over the last four years. The psychoeducation program was created to improve the daily capability in patients with BD. During sessions, patients are trained in strategies to be applied in their daily routines, as well as coping with stressful situations that present themselves as triggers for new crises. The treatment of these patients includes pharmacotherapy combined with psychoeducation, and some of them have psychological interventions [38];[39];[40]. The psychiatric diagnosis of BD patients for types I/II was defined in the Manual Diagnosis and Statistics of Mental Disorders (DSM-V), and confirmed by Semi-Structured Clinical Interview, according to DSM-V (SCID-5-CV). Manic and depressive symptoms were assessed using the Young Mania Rating Scale (YMRS) (Young et al. [41] and the 17 items version of the Hamilton Depression Rating Scale (HAMD-17) (Hamilton, [42], respectively. With HAM-17 scale, were evaluated depressive symptoms that had occurred within the last week, and in YMRS, manic symptoms that had presented themselves within the last 48h. The cutoff scores used in the study were: YMRS > 7 as indicative of mania and, HAMD-17 > 8 as indicative of depression. This selection was made to minimize the bias of symptomatology on psychosocial functioning, which has been widely proven in the literature.

2.3 Criteria

The inclusion criteria of bipolar patients in the euthymic stage were: (a) the patients had been in euthymic phase at least six months (b) active age (18 - 60 years); (c) none of the patients had a history of addiction or substance abuse

in last year; (d) no history of neurodegenerative diseases, cancer, morbid obesity or trauma (e) patients had no significant comorbid medical conditions, and did not receive medication in addition to those prescribed for their psychiatric condition; these should have been used for at least four weeks; (f) non-smokers (g) not pregnant or breastfeeding (h) patients were able to understand the procedures and protocol and provided written informed consent, and did not present cognitive impairment with disability or dementia, physical disabilities, e.g., visual or hearing impairing.

Healthy controls were selected among hospital staff, and the subjects were matched for demographic parameters of age, gender, education, and marital status. The inclusion criteria of healthy control patients were: (a) active age (18 – 60 years); (b) no diagnosis of BD confirmed by semi-structured clinical interview (SCID-5-CV) (c) no family history of severe mental illness such as schizophrenia, psychotic disorder, major depressive disorder, and BD in first-degree relatives (d) none of the patients had a history of addiction or substance abuse in the last year; (e) patients had no significant comorbid medical conditions and had not received medication for at least four weeks; (f) no history of neurodegenerative diseases, cancer, morbid obesity or trauma (g) non-smokers (h) not pregnant or breastfeeding (i) patients were able to understand the procedures and protocol and provided written informed consent, and did not present cognitive impairment with disability or dementia, physical disabilities, e.g., visual or hearing impairing.

2.4 Demographic, Clinical and Pharmacological Data

All this data was systematically obtained and included in the study. Demographic variables were age, gender, marital status, education level, employment situation, and years of education. Clinical variables were age at onset, illness duration (years), hospitalization and the duration of hospitalizations, suicide attempts, relatives' antecedents of mental diseases and participation in a psychoeducation group. Also, some psychometric tests were included to observe the following: to assess the manic symptoms we used the Young Mania Rating Scale (YMRS), and to evaluate the depressive symptoms we assessed the 17 items version of the Hamilton Depression Rating Scale (HAMD-17). To obtain information about functional impairment, we used the Functioning Assessment Short Test (FAST), and to assess frontal lobe functions we used Frontal Assessment Battery (FAB).

2.5. Neuropsychological Assessment

2.5.1. Functioning Assessment Short Test (FAST) and Frontal Assessment Battery (FAB)

In recent years, there has been an essential advancement in clinical measurements that analyze the deterioration of superior functions and in the functional impairment. However, these measurements are elaborated, specialized, exhaustive, and expensive. Thus, more straightforward tests like FAB and FAST help to measure cognitive performance and serve as a screen for further evaluation. In this research, we tried to establish the degree of functional impairment through FAST, and the EF through FAB, analyzing a group of BD I/II patients in their euthymic phase, compared with a healthy control group.

2.5.2. Functioning Assessment Short Test (FAST)

FAST is a tool developed to evaluate functional impairment and has been validated in different populations [43];[44];[36];[45]; [46];[47], and ages [48];[49] in BD patients. An analysis of the FAST psychometric properties showed optimal values of inter-observer reliability between two independent evaluations, differing one week from each other (mean $K = 0.73$). The internal consistency obtained was remarkably high, and the Cronbach's alpha was 0.955. There was also a highly significant negative correlation with the Global Assessment of Functioning (GAF) ($r = -0.9$; $p < 0.001$), pointing to a reasonable degree of concurrent validity [50].

The FAST scores are evaluated through six functional domains: **Autonomy** (the capacity to make decisions and do things by oneself); **Occupational Functioning** (the capacity to maintain a paid job, the efficiency of performing tasks at work, working in the field in which the patient was educated and earning according to the level of the employment position); **Cognitive Functioning** (the ability to concentrate, perform simple mental calculations, solve problems, and learn and recall new information); **Financial Issues** (the capacity to manage one's finances); **Interpersonal Relationships** (relations with friends and family, involvement in social activities, sexual relationships and the ability to defend one's interests), and **Leisure Time** (the capacity to engage in sports or physical activities and to enjoy hobbies). Four categories were established in the FAST scale of functional impairment cut-offs. No impairment: from 0 to 11 in the FAST total score. Mild impairment: from 12 to 20 in the FAST total score. Moderate impairment: from 21 to 40 in the FAST total score, Severe impairment: scores above 40 in the FAST total score.). However, patients are not static in a category after an intervention, either pharmacological or psychological, patients can interchange through categories [44];[51].

2.5.3. The Frontal Assessment Battery (FAB)

The Frontal Assessment Battery (FAB) is a brief (10-min) test of EF, consisting of six cognitive tasks that was

developed specifically to assess the frontal lobe functions. An analysis of the FAB psychometric properties showed optimal values of inter-observer reliability ($k = 0.87$; $p < 0.001$), an acceptable internal consistency (Cronbach's alpha = 0.78), and an ability to distinguish between patients and controls of 89% [52];[53]. In our research, we used the Brazilian version of FAB. This battery consists of six subtests which are: **Similarities** (explores the domain of abstract reasoning/conceptualization) i.e., to identify the link between two objects from the same semantic category (an apple and a banana are both fruits). **Lexical Fluency** (letters) (explores the domains of self organized strategy and shifting i.e., mental flexibility) where patients produce as many words as they can, beginning with the letter "S" in one minute. **Motor Series** (explores the domain of motor programming/planning). "Fist-edge-palm" series must be performed six times consecutively and spontaneously with their dominant hand. **Conflicting Instruction** (explores the domain of sensitivity to interference). It provides an opposite response to the examiner's alternating signal, e.g. tapping once when the examiner taps twice and vice versa, the single and double tapings are intermixed in a fixed order. Verbal commands conflict with sensory information and subjects should obey initial verbal command and refrain from following what they see. **Go-No Go Task** (explores the domain of inhibitory control and assesses the ability to withhold a response, inappropriately induced by both previous learning and concomitant sensory information). The same alternating signals used in the previous subtests are again given, but the subjects must now provide different responses, e.g., not tapping when the examiner taps twice and copying the examiner when he taps once. **Prehension Behaviour** (explores the domain of environmental independence). The examiner touches both palms, without saying anything or looking at the subject. If the subject spontaneously takes the hands, it means that sensory stimuli and environmental cues can activate patterns of responses that are normally inhibited [54]. The maximum score for each subtest is three points (with higher scores indicating better performance), and the total score of the test is calculated by adding the scores of the six subtests (maximum score = 18). Any performance score of 18 to 15 indicates a frontal lobe without disabilities. A performance of 14 to 11 is considered a moderate impairment and below 10 is considered a severe impairment. These score cutoffs were validated to a Portuguese population [54].

The FAB test can provide an easier, more reliable, and quicker measure of EF, useful in initial assessments, or when available time and resources are limited. Considering the multifaceted nature of EF, several tools were used to evaluate them, which presented good psychometric

properties, namely good internal consistency, and inter-rater reliability. Tests such as Frontier Executive Screen (FES), Executive Interview-25 (EXIT- 25), and Ineco Frontal Screening (IFS), have shown similar correlation and accuracy in detecting executive deficiencies in various pathologies, just as we observed in the FAB test. However, we know that there is a variability in the different tests concerning the specificity for some of the different EF measured, in different pathologies[55]. Nevertheless, this specificity is still low and has been pointed out as a limitation. Only the FAB and IFS tests presented normative studies, (performance compared to population data matched for age and education). Another issue is the relative usefulness of these executive screening tools in the different stages of neurodegenerative diseases, since the progression generally occurs towards generalized deficits [56]. Thus, the tests above can be useful for the differential diagnosis in the early stages of the disease (when combined with other measures), while their contribution in later stages may be more related to the description of the neurocognitive phenotype.

Although FAB was initially validated in patients with neurodegenerative diseases, and was later extended to other pathologies such as extrapyramidal disorders, vascular damage such as a stroke, dementia such as Alzheimer's disease, and frontotemporal dementia [52];[57];[58];[54];[59]; more recently, different authors have started to research the use of the FAB test for psychiatric diseases [60]; [61]; [62]; [63]; [64]. Regarding psychiatric illnesses, only EXIT-25 and FAB test can evaluate the cognitive tasks and be associated with specific areas of the frontal lobes (that is, able to measure, i.e., conceptualization with the dorsolateral areas, word generation with the medial areas, and inhibitory control with the orbital or medial areas, just as the FAB test was able to exhibit a degree of sensitivity to focal lesions near the anterior insula in the middle right lower frontal gyrus, and in the lower right frontal gyrus), [65];[66], but, it will be discussed forward.

2.6. Statistical analysis

Demographic and clinical variables were analyzed using descriptive statistics, including (mean), and (standard deviation) for quantitative variables and absolute frequency (n), and relatives (%), for qualitative variables with a confidence interval of 95% in both cases. For the qualitative nominal and ordinal data, we used the Chi-square test (χ^2) of Pearson and for two or more groups, we used Fisher's exact test. Parametric and nonparametric tests were used for the analysis of qualitative variables. The assumption of normality and homoscedasticity of each variable was analyzed with the Kolmogorov-Smirnov

normality test and Levene's test, respectively. For comparisons of parametric variables between two groups, the Student *t*-test was used, and more than two groups the Tukey's test of analysis of variance (ANOVA) was used. To compare non-parametric variables between two and three independent samples, the Mann-Whitney tests and the Kruskal-Wallis tests were used, respectively. The Dunn's posthoc test was performed to peer comparisons in case the main effect were significant. For association analyses, Pearson correlation was used to test quantitative variables, and Spearman correlation for nonquantitative variables. In addition, we stratified our sample into five groups according to the level of graduation: illiterate, up to primary school, up to high school, graduate and postgraduate. The total scores of each test; FAST and FAB, were correlated with age and educational level. It is important to note that this battery of evaluation represents only the beginning of cognitive functions, and only specialists who are trained can give a diagnosis, if there are any executive dysfunctions. The most recent version of the SPSS software program (SPSS Inc., Chicago, USA) was used. To calculate the statistical power analyses we used the program - G*Power 3.1. Statistical significance was set at $p < 0.05$ for all tests or adopting a level of significance of 5% to reject the null hypotheses.

III. RESULTS

3.1. Demographic, Clinical and Pharmacological Characteristics

The demographic and clinical characteristics of the different groups studied were evaluated. The sample included 25 healthy controls, and 50 patients with BD. Initially, it was calculated the sample size - difference between two independent means (two tails). The analyses showed an effect size $d = 0.853$; $\alpha = 0.05$; power ($1 - \beta$ err prob) = 0.80; noncentrality parameter $\delta = 2.89$; critical $t = 2.01$; $Df = 44$; sample size group 1 = 23; sample size group 2 = 23; total sample size = 46; actual power = 0.808.

Thirty-six (72%) were female. The healthy control had a mean age of (36.1 ± 9.87) and the euthymic patients analyzed had a mean age of (41.1 ± 11.05) years. Utilizing the *t*-test, the means of healthy controls and euthymic patients did not differ between ages ($t = 2.35$; $F = 1.254$; $p > 0.05$) and utilizing the Chi-square test, there was no difference in gender ($p > 0.05$). There were no significant differences between groups in marital status. However, it was observed after performing the Chi-square test followed by the Fisher's exact test, that the groups significantly differed in terms of their educational level ($p < 0.01$), and occupational status ($p < 0.02$). The mean years of education were (14.7 ± 2.18) years in healthy

controls, and (13.1 ± 2.80) years in euthymic patients. After performing the t-test followed by the Mann Whitney test, the groups significantly differed in terms of years of education ($t=2.52$; $U=418.5$; $p<0.02$). Eight (16%) of patients studied at primary school, 21 (42%) at high school, 21 (42%) had university graduation, and no one with postgraduate education (**Table 1.**)

The bipolar patients had a mean of illness duration of (8.24 ± 7.65) years, and the mean age at onset of illness was (23.1 ± 7.01) years. Seventeen (34%) patients had previously been hospitalized. Among the hospitalized patients, the mean duration of hospitalization was $(13.2 \text{ days} \pm 0.967)$, and eighteen (36%) patients attempted suicide. The family history of BD was positive in 24 (48%) patients. Regarding pharmacologic treatment, our results showed that 10 (20%) of the patients were on monotherapy. Among the patients on polypharmacy, 18

(36%), 16 (32%), and 6 (12%) of the patients received 2, 3, and 4 psychotropic medications, respectively. The percentages of mood stabilizers, antipsychotics, antidepressants, and benzodiazepines used in patients according to their clinical symptoms, are presented in **Table 2.** To evaluate the absence of depression or mania in the samples, the HAM-D and YMRS tests were used in the healthy control group, and in the euthymic patients' group respectively. The observed results had a mean HAM-D score of (4.32 ± 2.40) for healthy control, and (3.88 ± 1.75) for euthymic patients. After performing the t-test, the groups did not differ ($t = 0.88$; $F=2.016$; $p > 0.05$). Regarding a mean YMRS score, the mean was (0.64 ± 0.90) to healthy control and (0.98 ± 1.02) to euthymic patients. After performing the t-test the groups did not differ ($t = 1.41$; $F=1.263$; $p > 0.05$) as seen in the **Table 2.**

Table 1: Sociodemographic Characteristics of the Sample

	Healthy Controls n = 25	Bipolar Patients n = 50	p - Value
Age, years ^b	35.0 (9.96)	41.1 (11.02)	$P = 0,52^c$
Gender, n			$P = 0,43^a$
Male	9	14	
Female	16	36	
Marital status n (%)			$P = 0,55^d$
Married	12 (48.0)	24 (48.0)	
Divorced	1 (4.0)	7 (14.0)	
Widowed	1 (4.0)	1 (2.0)	
Single	11 (44.0)	18 (36.0)	
Education n (%)			$P < 0,01^d$
Illiterate	-	-	
Up to primary school	0 (0.0)	8 (16.0)	
Up to high school	10 (40.0)	21 (42.0)	
Graduate	12 (48.0)	21 (42.0)	
Postgraduate	3 (12.0)	0 (0.0)	
Years of education ^b	14.7 (2.18)	13.1 (2.80)	$p < 0,02^e$
Work situation n (%)			$P < 0,02^d$
Employed	23 (92.0)	30 (60.0)	
Unemployed	2 (8.0)	17 (34.0)	
Medical benefits	0 (0.0)	2 (4.0)	
Invalidity	0 (0.0)	1 (2.0)	

^a χ^2 ^b Mean (SD) ^c t test ^d Fisher's exact test ^e Mann Whitney

Table2: Clinical and Pharmacological Characteristics of the Sample

	Healthy Controls n = 25	Bipolar patients n = 50	p- Value
Illness duration (years) ^a	N/A	8.24 (7.65)	
Age of onset (years) ^a	N/A	23.1 (7.01)	
HAM-D total score ^a	4.32 (2.49)	3.88 (1.75)	$p = 0.50$ ^b
YMRS total score ^a	0.56 (0.86)	0.98 (1.02)	$p = 0.08$ ^b
FAST score ^a	9.80 (5.94)	25.10 (11.08)	$p < 0.001$ ^c
FAB score ^a	15.72 (1.64)	13.56 (2.81)	$p < 0.001$ ^c
Hospitalizations n (%)	N/A	17 (34)	
Duration hospitalizations (day) ^a	N/A	13.20 (30.7)	
Suicide attempts n (%)	N/A	18 (36)	
Family history of affective disorders n (%)	N/A	24 (48)	
Psychoeducation Yes, n (%)	N/A	42 (84)	
Treatment n (%)			
Lithium	N/A	29 (58)	
Other mood stabilizers	N/A	22 (44)	
Atypical antipsychotics	N/A	19 (38)	
Typical antipsychotics	N/A	4 (8)	
Antidepressants	N/A	14 (28)	
Benzodiazepines	N/A	11 (22)	

HAM-D 17 = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale; N/A = not available

^a Mean (SD) ^b *t* test ^c Mann Whitney

3.2. Functional Status and Neurocognitive Performance.

3.2.1. Healthy Controls versus Euthymic Patients

The results of the general functional and cognitive assessments were measured by performing the FAST and FAB tests (mean \pm SD) for healthy control and euthymic patients, respectively. The means of the FAST test were (9.80 \pm 5.94) and (24.6 \pm 11.15), respectively; and it was observed after performing the *t* test followed by the Mann Whitney test ($t = 6.195$; $U = 126$; $p < 0.001$). The means of the FAB test were (15.72 \pm 1.64) and (13.68 \pm 2.61), respectively and the results were observed after performing the *t* test followed by the Mann Whitney test (t

$= 3.567$; $U = 310$; $p < 0.001$). Through the FAST and FAB tests, we concluded that the patients with BD had greater functional and cognitive impairment than healthy controls, as seen in the **Table 2 and Figs.1-2**. Our results are compatible with other research performed [44];[50];[45];[67].

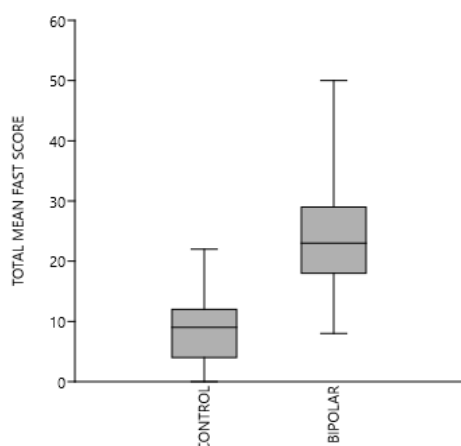


Fig.1. Mean (SD) Total Functioning Assessment Short Test (FAST) Scores between Healthy Control and Patients

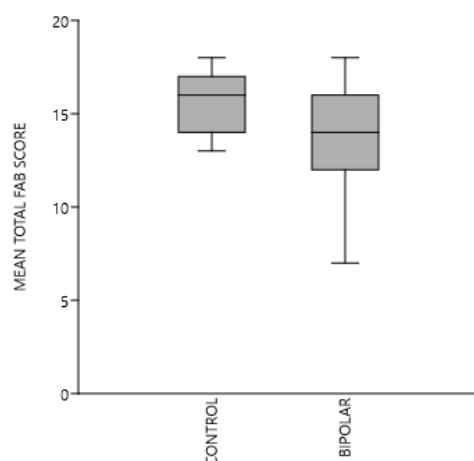


Fig.2. Mean (SD) Total Functioning Assessment Short Test (FAB) Scores between Healthy Control and Patients.

Table 3: Mean Total of FAST and FAB Scores in Health Controls and Euthymic Patients with ≤ 40.5 and ≥ 40.5 years old

	Healthy Control <i>n</i> =25	Euthymic Patients <i>n</i> = 50 <i>n</i> =25 each group	<i>t</i>	<i>U</i>	<i>p</i>	<i>d</i>	<i>r</i>
1. Means (\pm SD)FAST < 40.5 y	9.27 (\pm 4.84)	23.9 (\pm 10.01)	6.035	39.0	< 0.001**	-1.860	-0.681
2. Means (\pm SD)FAST > 40.5 y	11.14 (\pm 8.47)	24.9 (11.51)	2.622	30.5	< 0.001**	-1.361	-0.562

3.2.2. FAST and FAB score and age

Based on these results, our group decided to divide the samples into two groups by age. For this purpose, we used the median age of the patients (median = 40.5 years). Twenty-five patients were younger than 40.5 years old, and 25 patients were older than 40.5 years old. We used the same method with the control group, and the following results were observed. The results of the FAST and FAB tests were demonstrated (mean \pm SD) to each median (\leq and \geq 40.5 years old), for control and euthymic patients groups, respectively.

The (means \pm SD) of FAST scores between the healthy control group and the euthymic group in a median ≤ 40.5 and ≥ 40.5 years old were (9.27 \pm 4.84), (23.9 \pm 10.01) and (11.14 \pm 8.47), (24.9 \pm 11.51) respectively. After performing the *t*-test followed by the Mann Whitney test, the groups differed in age (*t* = 6.035; *U* = 39.0; *p* < **0.001**) and (*t* = 2.622; *U* = 30.5; *p* < **0.001**), respectively. The (means \pm SD) of FAB scores between the healthy control group and the euthymic group in a median ≤ 40.5 and ≥ 40.5 years old were (15.72 \pm 1.63), (14.0 \pm 2.99) and (15.71 \pm 1.79), (13.2 \pm 2.62), respectively. After performing the *t*-test followed by the Mann Whitney test, the groups differed in age (*t* = 2.261; *U* = 139.5; *p* < **0.01**) and (*t* = 2.406; *U* = 36.5; *p* < **0.001**), respectively, as seen in the Table 3.

3. Means (\pm SD) FAB \leq 40.5 y	15.72 (\pm 1.63)	14.0 (\pm 2.99)	2.261	139.5	< 0.01**	0.714	0.336
4. Means (\pm SD) FAB \geq 40.5 y	15.71 (\pm 1.79)	13.2 (\pm 2.62)	2.406	36.5	< 0.001**	1.118	0.488
FAST total score	9.80 (\pm 5.94)	24.60 (\pm 11.09)	6.34	3.24	0.001	-1.663	-0.693
FAB total score	15.72 (\pm 1.64)	13.56 (\pm 2.81)	3.56	2.50	0.001	0.938	0.424

Note. Means \pm standard deviation (SD). FAB = Frontal Assessment Battery FAST = Functioning Assessment Short Test.[*] indicate FAB and FAST scores significantly different between groups by t-test (*t*)and followed by Mann–Whitney test (*U*) for independent samples, *d* = Cohen’s effect size. ***p* < 0.01

However, when comparing the FAST group and FAB group with age between (\leq 40.5 and \geq 40.5 years old) we did not observe any significant difference, as shown in **Figs.3-4**. The means of the age of the FAST groups with median \leq 40.5 and \geq 40.5 years old, were (23.9 ± 10.06), and (24.9 ± 11.51), respectively. After performing the *t*-test followed by the Mann Whitney test, the groups did not differ in age (*t*=0.340; *U*= 295.5; *p* > 0.05). The means of the age of the FAB groups were (13.9 ± 2.98), and (13.1 ± 2.62), respectively. After performing the *t*-test followed by the Mann Whitney test, the groups did not differ in age (*t*=0.955; *U*= 268.5; *p* > 0.05), as seen in **Figs.3-4**.

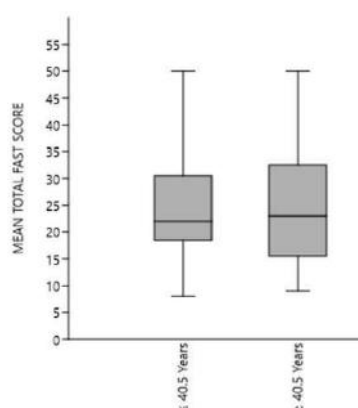


Fig.3. Mean Total of FAST Scores in Euthymic Patients with \leq 40.5 and \geq 40.5 years old

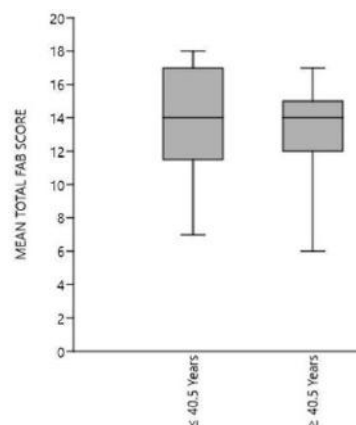


Fig.4. Mean Total of FAB Scores in Euthymic Patients with Median \leq 40.5 and \geq 40.5 years old

Thus, it was observed that the euthymic patients had greater functional (FAST) and frontal cognitive (FAST) impairment than healthy controls, in both groups (\leq 40.5 and \geq 40.5 years old). Nevertheless, when we compared the groups FAST (\leq 40.5 and \geq 40.5 years old) and FAB

(≤ 40.5 and ≥ 40.5 years old) we did not observe any significant difference between them. Thus, in this study, it showed that to be younger or older (age ≤ 40.5 years and ≥ 40.5 years), did not differ from the total scores of the FAST and FAB tests.

3.2.3. FAST and FAB score and years of study

In addition to age, another point that was assessed by our study and which may interfere in the FAST and FAB results, is the number of years spent studying. Various authors observed that the study time could influence the test results [70];[68];[69]. Our samples (healthy control and euthymic patients) presented a study time variation between (8 to 18 years). Based on these values, our group decided to divide the samples into two groups. For this purpose, we used the median of study time (median = 12 years) (≤ 12 years of study and > 12 years of study). Twenty-seven euthymic patients studied ≤ 12 years and 23 euthymic patients studied > 12 years. We used the same method with the control group, and the following results were observed. The results of the FAST and FAB tests were demonstrated (mean \pm SD) to each median (≤ 12 and > 12 years), for control and euthymic patients groups, respectively. As previously described above, see **Table 1**, after performing the t -test followed by the Mann Whitney test, the groups in study time differed significantly between healthy control (14.7 ± 2.18) and euthymic patients (13.1 ± 2.80); ($t = 2.52$; $U = 418.5$; $p < 0.02$).

However, the (means \pm SD) of FAST scores between the healthy control group and the euthymic patients' group in a median ≤ 12 years were (11.7 ± 7.76) and (27.4 ± 12.72) respectively. After performing the t -test the groups differed in study time ($t = 3.10$; $F = 2.687$; $p < 0.003$). The means of FAB scores between the healthy control group and the euthymic patients' group in a median ≤ 12 years were (15.8 ± 1.06) and (13.5 ± 2.77) respectively. After performing the t -test the groups differed in study time ($t = 2.16$; $F = 6.755$; $p < 0.03$). The (means \pm SD) of FAST scores between the healthy control group and the euthymic patients' group in a median > 12 years were (9.1 ± 5.15) and (21.3 ± 8.01) respectively. After performing the t -test the groups differed in study time ($t = 5.61$; $F = 2.42$; $p < 0.001$). The (means \pm SD) of FAB scores between the healthy control group and the euthymic patients' group in a median > 12 years were (15.8 ± 1.73) and (13.4 ± 2.98) respectively. After performing the t -test the groups differed in study time ($t = 52.97$; $F = 2.995$; $p < 0.01$), see **Table 4 – 5**.

Table 4: Mean Total of FAST and FAB Scores in Healthy control and

Euthymic Patients with Median ≤ 12 years of study

	Healthy Control (MEANS \pm SD)	Euthymic Patients (MEANS \pm SD)	t	F	p
FAS T	11.7 \pm 7.76	27.4 \pm 12.72	3.103	2.687	< 0.003**
FAB	15.8 \pm 1.06	13.5 \pm 2.77	2.16	6.755	< 0.03*

Table 5: Mean Total of FAST and FAB Scores in Healthy control and Euthymic Patients with Median > 12 years of study

	Healthy Control (MEANS \pm SD)	Euthymic Patients (MEANS \pm SD)	t	F	p
FAS T	9.1 \pm 5.15	21.3 \pm 8.01	5.61 1	2.42 0	< 0.001**
FAB	15.8 \pm 1.73	13.4 \pm 2.98	2.97	2.99 5	< 0.01*

However, when compared the FAST groups (≤ 12 years and > 12 years), and FAB groups (≤ 12 years and > 12 years), we did not observe any significant difference as shown in **Figs.5-6**. The means of the years of study of the FAST groups with median ≤ 12 and > 12 years of study, were (27.4 ± 21.2), and (21.2 ± 8.01) respectively. After performing the t -test, the groups did not differ in time of study ($t = 1.901$; $F = 2.865$; $p > 0.05$). The means of the years' study of the FAB groups with median ≤ 12 and > 12 years, (13.5 ± 2.77), and (13.4 ± 2.98) respectively. After performing the t -test followed by the Mann Whitney test, the groups did not differ in time of study ($t = 0.049$; $F = 1.152$; $p > 0.05$) see **Figs.5-6**.

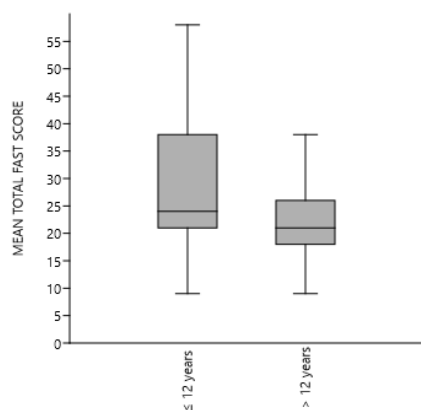


Fig.5. Mean Total of FAST and FAB Scores in Healthy control and Euthymic Patients with Median ≤ 12 years of study

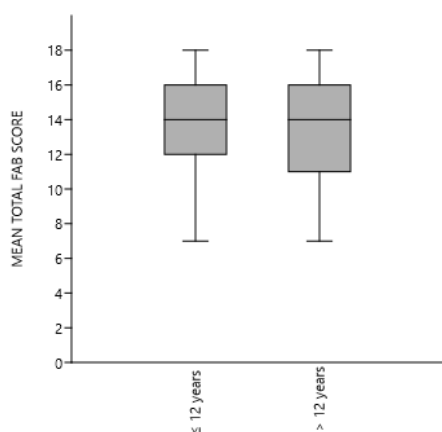


Fig.6. Mean Total of FAST and FAB Scores in Healthy control and Euthymic Patients with Median > 12 years of study

Thus, in this study, it demonstrated that years of study showed that less (≤ 12 years of study) or more (> 12 years of study), did not differ from the total scores of the FAST and FAB tests.

3.2.4. Categories Scores of FAST and FAB tests in Healthy Controls and Euthymic patients

As mentioned above, FAST and FAB tests have different scoring categories. These different categories demonstrate a greater or lesser severity in the patient's functionality in their daily life (FAST) and impairment or not in his frontal cognitive activity. The **Table 6**, demonstrates that 88% ($n = 44$) of the patients had overall functional impairment (defined as a FAST total score > 11) compared to 28 % ($n = 9$) of the control group ($p < 0.001$). There was a predominance of the first category in the total FAST scale (0 to 11 - no impairment) ($n = 18$; 72%), in the control group. However, in the bipolar patients, there was a predominance of the third category in the total FAST scale (21 to 40 - moderate impairment) ($n = 30$; 60%). For the analysis of nominal and ordinal qualitative data, Pearson's chi-square test (χ^2) was used for two or more groups. The results showed that there was a significant difference in the four categories between the control group and the bipolar patients, in the FAST test ($p < 0.001$). On the other hand, **Table 7**, demonstrates that there was a predominance of the first category in the total FAB scale (18 to 15 - no impairment) ($n = 18$; 72%), in the control group. However, in the bipolar patients, there was a predominance of the second category in the total FAB scale (14 to 11 - moderate impairment) ($n = 26$; 52%). For the analysis of nominal and ordinal qualitative data, Pearson's and chi-square test (χ^2) were used for two or more groups. The results showed that there was a significant difference in the three categories between the control group and the bipolar patients, in the FAB test ($p < 0.001$). Thus, both, the FAST and the FAB groups showed a moderate impairment in functionality and EF.

Table 6: FAST total scale and the categories of functional impairment cut-offs

	Healthy Control N = 25	Bipolar patients N = 50	p - Value
FAST score			$p < 0.001^a$
0 - 11 No impairment	18	6	
12 - 20 Mild impairment	5	9	
21 - 40 Moderate impairment	2	30	
41 - 60 Severe	0	5	

impairment**(FAST)Functioning Assessment Short Test** ^a χ^2 followed by Fisher's exact test

Table 7: FAB total scale and the categories of cognitive impairment cut-offs

	Healthy Control N = 25	Bipolar patients N = 50	p - Value
FAB score			p < 0.01 ^a
18 - 15 No impairment	18	18	
14 - 11 Moderate impairment	7	26	
10 - 0 Severe impairment	0	6	

(FAB)Frontal Assessment Battery ^a χ^2 followed by Fisher's exact test

3.2.5. Categories Scores of FAST test in Healthy Controls and Euthymic patients

Significant differences were found in all distinct domains of the FAST test between euthymic patients and healthy controls, ($p < 0.05$), as seen in the **Fig.7**. Specifically, patients showed decreased in occupational, autonomy, cognitive and interpersonal domains, had the most significant differences ($p < 0.001$), suggesting that these domains may be the most impaired. All effect sizes (d) were in the same direction, suggesting worse performance in the patient group than in the healthy control, see **Table8**.

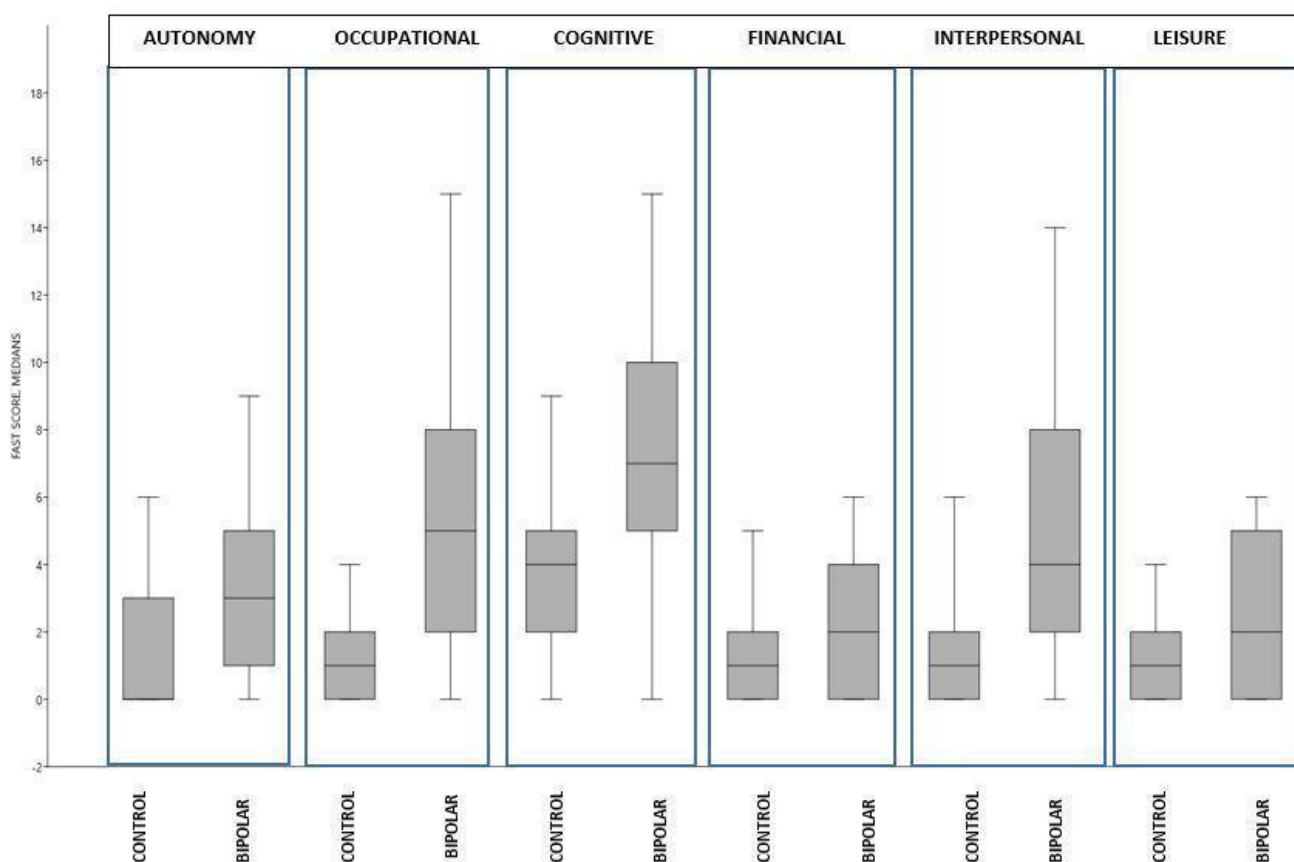


Fig.7. Mean Functioning Assessment Short Test (FAST) Domain Scores and Healthy Controls

Table8: Neurocognitive functioning as assessed by the FAST in Bipolar Patients

<i>FAST Subtest</i>	CONTROL GROUP n=25	BIPOLAR GROUP n= 50	<i>t</i>	<i>F</i>	<i>p</i>	<i>d</i>	<i>r</i>
<i>1. Autonomy</i>	1.20 (±1.76)	3.24 (±2.61)	3.52	2.20	0.001*	-0.916	-0.416
<i>2. Occupational Functioning</i>	0.96 (±1.10)	5.32 (±4.24)	5.03	14.93	0.001**	-1.407	-0.575
<i>3. Cognitive Functioning</i>	4.00 (±2.25)	7.50 (3.66)	4.37	2.63	0.001**	-1.152	-0.499
<i>4. Financial Issues</i>	1.32 (±1.49)	2.32 (±2.01)	2.19	1.82	0.04*	-0.565	-0.271
<i>5. Interpersonal Relationship</i>	1.24 (±1.56)	5.12 (±4.10)	4.55	6.90	0.001**	-1.250	-0.530
<i>6. Leisure Time</i>	1.20 (±1.22)	2.62 (±2.23)	2.96	3.31	0.01*	-0.790	-0.367
<i>FAST total score</i>	9.80 (±5.94)	24.60 (±11.09)	6.34	3.24	0.001**	-1.663	-0.693

Note. Means ± Standard Deviation (SD). FAST = Functioning Assessment Short Test. Analysis of FAST subtests scores by t-test (*t*) (*F*) for independent samples, *d* = Cohen's effect size. **p* < 0.01 and ***p* < 0.001.

3.2.6. Categories Scores of FAB test in Healthy Controls and Euthymic patients

In the original FAB test, Dubois et al. [52] produced a theoretical construct, suggesting a two-factor structure of the FAB test. The two-factor are composed of cognitive and behavioral aspects. The first factor is assigned as a **cognitive control factor**, which includes the **Conceptualization; Mental Flexibility, and Inhibitory Control** subtests. These three subtests primarily examine abilities related to performing mental operations (such as verbal abstraction and inhibition of inappropriate responses). The second factor is assigned as a **behavioral control factor**, which includes **Motor programming, Sensitivity to interference, and Environmental autonomy** subtests. These three subtests mainly evaluate the abilities of motor regulation, such as

motor sequencing and withholding of automatic movements. In the present study, our results, in addition to reinforcing this construct, can observe that two subtests that characterize the cognitive control factor (**Conceptualization and Inhibitory Control**) showed significant changes (*p* < 0.05). All effect sizes (*d*) were in the same direction, suggesting worse performance in the patient group than in the healthy control. Nevertheless, only one subtest related to behavioral control factor (**Sensitivity to interference**) showed a significant difference between groups (*p* < 0.01) as we can see in **Table 9**. Thus, in this study, we observed that the impact of the BD, even in patients in the euthymic phase becomes present in factors related to cognition and motor factors [71], as seen in the **Table9**.

Table 9: Neurocognitive functioning as assessed by the FAB in Bipolar Patients

FAB Subtest	CONTROL GROUP n=25	EUTHYMIC GROUP n= 50	t	F	p	d	r
1. Similarities (Conceptualization)	1.84 (±0.85)	1.34 (±1.08)	2.01	1.61	0.041*	0.514	0.249
2. Lexical Fluency (Mental flexibility)	2.72 (±0.46)	2.50 (±0.61)	1.58	1.79	0.147	0.407	0.197
3. Motor Series (Motor programming)	2.92 (±0.28)	2.64 (±0.72)	1.86	6.79	0.064	0.512	0.248
4. Conflicting Instruction (Sensitivity to interference)	2.92 (±0.54)	2.52 (±0.76)	2.53	7.58	0.013*	0.606	0.290
5. Go-No Go Task (Inhibitory control)	2.32 (±1.14)	1.50 (±1.46)	2.45	1.62	0.026*	0.626	0.298
6. Prehension Behaviour (Environmental autonomy)	3.00 (±0.00)	2.94 (±0.42)	0	0	0.498	0.202	0.100
FAB total score	15.72 (±1.64)	13.56 (±2.81)	3.56	2.50	0.001	0.938	0.424

Note. Means ± Standard Deviation (SD). FAB = Frontal Assessment Battery. Analysis of FAB subtests scores by t-test (t) (F)for independent samples, d = Cohen's effect size. * $p < 0.05$.

3.3. Correlation between FAST and FAB tests scores in euthymic patients

The **Fig.8** displays the impact of cognitive function (FAB test) of euthymic patients on functionality (FAST test). The correlation between frontal cognition and functionality was analyzed through the scores of the FAB and the FAST tests in euthymic and healthy control patients, using the Spearman Correlation Coefficient. Although only a small number of samples of euthymic patients were used (n=50) and healthy control (n=25), it was possible to observe a negative Spearman Correlation Coefficient, after assessing normality using the Shapiro-Wilk test. The correlation presented a moderate intensity ($r^2 = -0.539$) to euthymic patients and very weak correlation in healthy control ($r^2 = -0.106$). This correlation between the variables FAB and FAST, demonstrated that euthymic patients who have

lower scores on the FAB (decreased frontal activities and EF), had higher scores on the FAST (with greater loss of functionality). Since $r^2 = -0.539$, it represent a moderate correlation, and the FAB variable alone is not able to explain the total FAST variability. However, the sample results provide significant statistical evidence between FAB and FAST ($p < 0.0001$). Regarding the healthy control group, we did not find a significant correlation, ($p > 0.05$). Furthermore, it is important to remember that the correlation coefficient (r^2) is only an estimate of the population correlation coefficient (p), and we should not forget that the value of r is calculated based on some data pairs constituting random samples. Often the points in the sample may show a correlation, and even though the population does not, in this case, we are facing an inference problem, since $r \neq 0$ is not a guarantee that $p \neq 0$.

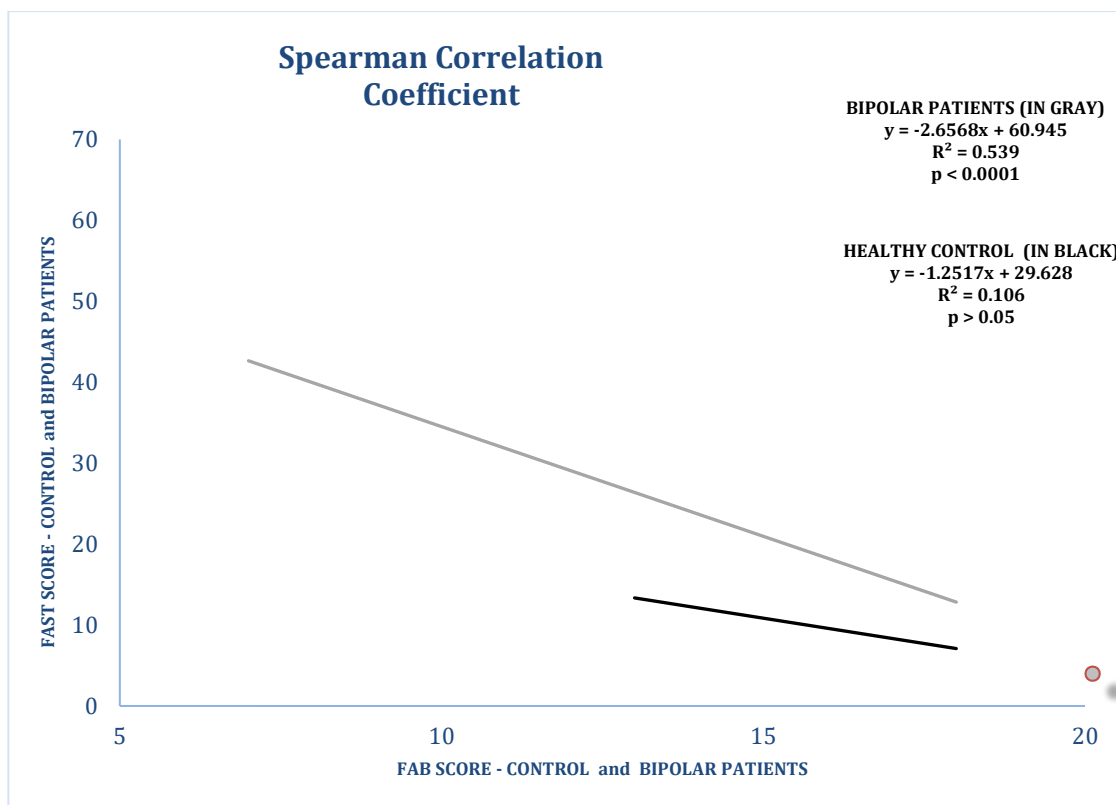


Fig. 8 .Correlation between FAST and FAB test scores in healthy control ($n= 25$) (in black) and euthymic patients ($n=50$) (in gray), using the Spearman Correlation Coefficient.

3.3.1. Correlation between years of education with FAST and FAB tests scores in euthymic patients

We analyze through a correlation test, the control group which presents a (mean \pm SD) years of education (14.72 ± 2.18) correlating with a mean total of FAST score (9.80 ± 5.94), and a mean total of FAB score (15.72 ± 1.64). We used the Spearman correlation coefficient test, and no significant correlation was found (FAST $r^2 = -0.21$ and FAB $r^2 = 0.06$, $p > 0.05$). Posteriorly, we evaluated 50 euthymic patients, which presents a mean years of education (13.1 ± 2.84 years, ranging between 8 to 19 years), correlating with the mean total FAST score (24.6 ± 11.15 , ranging between 8 to 58 score) and a mean FAB score (13.68 ± 2.61 score, ranging between 6 to 18 score). After the Spearman correlation coefficient test, no significant correlation was found related to the FAST scores and years of education ($r^2 = -0.018$; $p > 0.05$). However, we found a positive correlation between the years of education and FAB scores, ($r^2 = 0.326$; $p < 0.05$) by utilizing the Spearman coefficient test, see Figs.9-10.

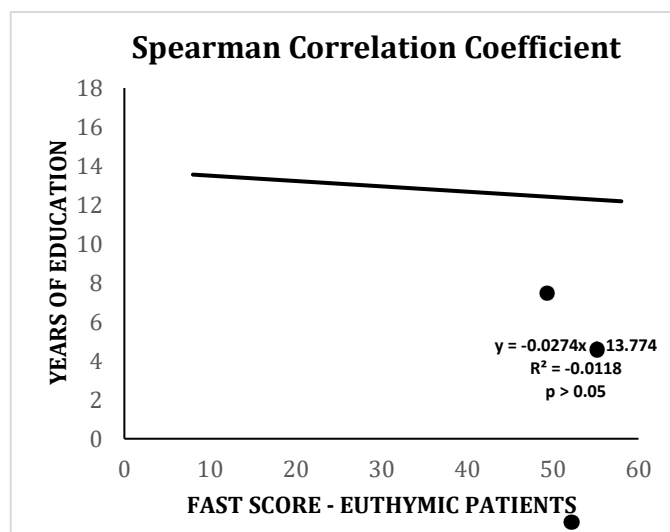


Fig.9. Correlation between years of education and FAST score of euthymic patients Linear regression $p > 0.05$; $r^2 = -0.011$.

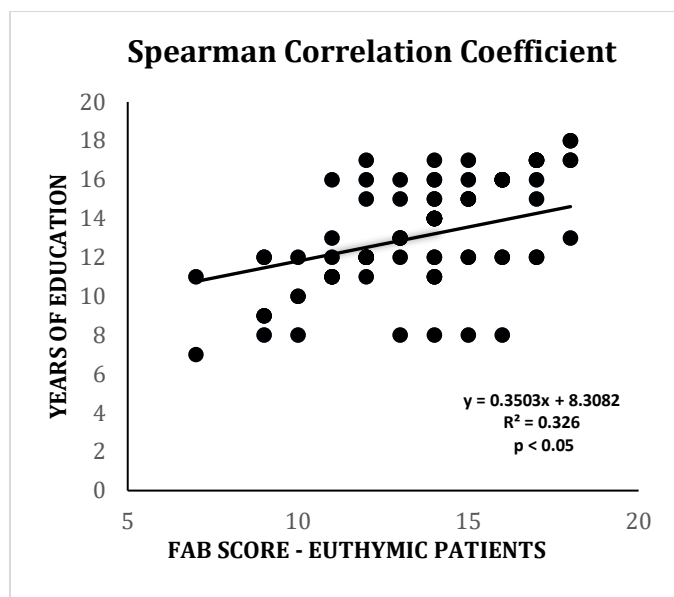


Fig.10. Correlation between years of education and FAB score of euthymic patients Linear regression $p < 0.05$; $r^2 = 0.326$.

IV. DISCUSSION

Since the beginning of this research, we have tried to apply standardized criteria for euthymia and the control group strictly. We wanted to reduce the biases related to this research, as much as possible. The safety measurements, criteria, and diagnosis of the disease, as well as the sample of bipolar patients who had been in the euthymic phase for at least six months, resulted in more accurate data. The rigor in the application of all the tests used by our highly trained staff eliminated any dubious interpretation or results of FAST and FAB. In a meta-analysis, [72], showed that many previous studies had not expressed this concern with standardization, producing a considerable variability in the results found [73]. Despite the meticulous application of the tests by the staff; some biases were still present, e.g., the small number of patients in each group, the heterogeneity of the population as well as their educational level, the diversity of medications used by patients, which may produce different effects on cognition. Another relevant point which was considered when analyzing the bipolar patients' cognitive abilities, was their age. Numerous age-related changes in cognitive abilities are significant to the everyday activities of the patients. According to [74], studies of the neurophysiological processes on cognitive performance have shown that cognitive skills reach their maximum point at the age of 30 and remain stable until they start to decline to 50 to 60 years old. Many studies demonstrated lower cognitive levels during aging [75]; [76]; [77]; [78]; [79]. This physiological decline

in senescence is due to neuro-anatomical changes that cause a degradation of the brain structure; however, this decline in cognitive functions is not uniform for all of them. Functions such as the ability to communicate through language, the use and definition of words; evocation and knowledge of general culture; practical or social reasoning; remain stable during their lives. However, they have difficulties in understanding long and complicated phrases, quickly recalling specific names or terms, sometimes generating a more repetitive speech; difficulty in understanding organized and logical analysis of unfamiliar or abstract material. Performance in the planning, execution, and evaluation of complex scales of behavior and performance of new and fast perceptual motor tasks, is also impaired [74]; [80]; [75]; [81]; [82]. For this reason, we only included patients with a maximum age of 60 years old, trying to reduce any bias related to the cognitive test results, both in the natural and pathological aging process.

Through this strict criteria adopted for the inclusion of bipolar patients in our study, we observed statistically significant results after applying the FAST and FAB tests that occurred both in the means (Figs.1-2), as well as in the different domains of the tests (Fig.7; Tables 8-9). In the FAST test, we analyzed an important decrease in the functional capacity of bipolar patients in all domains, which made us realize the impact of the disease on the patients' daily lives. These results are clearly related to previous literature studies, where several authors observed the same results [24]; [83]; [84]; [85]; [67]. Also, Bonnin et al. [25], assessed a total of 32 euthymic bipolar patients clinically and neuropsychologically at baseline. After an average 4-year follow-up, they were interviewed with the FAST test to assess functional outcomes. They observed that depressive symptomatology together with neurocognitive impairments related to verbal memory and EF are predictor variables of long-term functional outcome in BD. In a recent categorical meta-analysis which included 11 other studies, with a total sample of 1083 patients, the prevalence of global functional impairment was 58.6%. Regarding the specific domains, the meta-analysis presented an impairment prevalence in the following domains: 65.6% in the occupational, 49.2% in the cognitive, 42.6% in the autonomy, 42.1% in the interpersonal relationships, 29.2% in the leisure, and 28.8% in the financial issues domain - all of which were statistically significant [86]. In another study on the relationship between cognitive and occupational function in euthymic patients, it was reported that over six months, cognitive measures at the time of symptomatic recovery, particularly in the domains of working memory/attention and speed of processing, were strongly associated with

concurrent occupational recovery[87]. These findings suggest that a decline in cognitive function over time can be paralleled by a functional decline in occupation despite an euthymic state in bipolar disorder. We found very similar results in our research, which are presented in **Fig.7**, and they reinforce the idea that BD has a significant impact on the day to day functionality in these patients' lives.

Regarding the FAB test, and confirming one of our initial hypotheses, we observed the same phenomenon. The FAB test performance in our study presented significantly worse scores in the following domains: similarities (conceptualization), conflicting instructions (sensitive to interference), and go/no-go (inhibitory control), which demonstrated a significant executive dysfunction in bipolar patients (**Table 9**). However, since few studies up to date used the FAB test for patients with BD, we found it difficult to correlate our results with previous studies. For this purpose, we compared the results found in other studies, researching different psychiatric pathologies with altered EF, which also observed similar results [17];[18];[19]. Furthermore, our results differed from other studies that also evaluated the components of EF in euthymic patients with BD, and who performed poorly in mental flexibility, unlike our study [88];[89];[90]. Other domains such as inhibitory control [91], and conceptualization [29];[90], remained preserved in these studies, nevertheless were different from our results. Even so, our results are in line with previous studies demonstrating a substantial proportion of bipolar patients who experienced unfavorable general functioning, and that there is a significant degree of morbidity and dysfunction associated with BD, even during euthymic periods [37];[92].

Data from two meta-analyses demonstrated that cognitive changes persist during euthymia; even though there is a variation in the results concerning the domains involved, and the effect size produced [93];[16]. There are many discrepancies between authors regarding the performance in many different neuropsychological tests related to EF by bipolar patients. For example, patients in the manic phase may have difficulty adapting to conceptual changes, as can be seen in the Trail Making Test, as well as, during the depressive phases, demonstrating that bipolar patients have a poorer performance especially in verbal fluency tests, when compared with unipolar patients. Also, in the euthymic phase, changes in EF were observed with several persevering errors in the Wisconsin Card Sorting Test. Thus, using different tests, to assess the EF, it was observed that the degree of commitment and the size of the effect can be quite diverse between the various domains. In summary, different EF were not equally impaired in

euthymic BD patients [94];[95];[96]. It became significant in our research because we tried to evaluate the possible confounding variables that could interfere with the result found in the correlation between the FAB and FAST tests. A characteristic of the confounding variable is that it influences both the dependent and the independent variables, which can cause a spurious association. In our study, clinical variables such as (gender, age, length of illness), showed little effect on executive performance, except the study time, which showed some correlation with the FAB test as seen in the **Fig.10**, which will be discussed next. As previously described, this research showed particularly that less or more years of studying (≤ 12 years and > 12 years), did not differ from the total scores of the FAST and FAB tests. However, our study did not take into account some significant variables, as described by Shoeyen et al. [97], that observed that the main clinical variables that were significantly associated with lower levels of education in euthymic patients were associated with: the age of the first episode, the number of rapid cycling, and who had more than four depressive episodes. In our research, we found that the (mean \pm SD) of years of schooling completed was (14.7 ± 2.18) years for the healthy control group, and (13.1 ± 2.80) years for euthymic patients which were very significant difference ($p < 0.01$), see **Table 1**. Furthermore, the level of education was different between groups. While the control group had the majority of subjects (60%) with graduate and postgraduate education, the euthymic patients had (84%) up to high school and graduated with a significant difference ($p < 0.02$). Our findings were following a nationwide Danish register study [98], reporting lower educational levels in BD compared to the general population. In a survey that compared bipolar patients to healthy control, where IQ levels similar, it was observed that patients with BD completed fewer years of education than controls. Although more than 60% of both groups entered college, only 16% of bipolar patients received a university degree. In contrast, 47% of control patients completed college. Although the educational level did not differ between patients who started the disease earlier or later, nor due to substance abuse [99]. Another research demonstrated, that more education and shorter illness duration remained significantly associated with functional recovery. One more year of education was associated with a 1.45 times higher chance of functional recovery, and being ill one year longer was associated with a lower chance of functional recovery [100]. More recently, Baune and Malhi, [101], observed a slightly different result, where patients with BD had the same level of education, however, had a significantly lower social and occupational function than the general population.

Curiously, in our research we also observed a shorter time concerning the years of education in the bipolar patients, which produced a greater impact on occupational activities; as seen in the **Table 1**. Thus, the level of education is interrupted due to crises during BD, and the reduction in the level of education may contribute to the later functional disability in this disease. Thus, many studies showed that there is an inverse correlation between the degree of education with the social, occupational function, and risk of disability[102];[103];[104]. Also, other studies had shown that bipolar patients' household income was below 10%, and many of them were on disability pension in comparison with the general population, [105];[106];[98]. Thus, our results are according to literature reinforcing the previous studies.

Another variable related to cognitive functions and the functionality is age. It was interesting to note that our study was not associated with the loss of functionality and cognitive functions with the age of the patients, as can be seen in **Table 3; Figs.**

3-4. We found very significant differences between both the control group and euthymic patients after using the FAB and FAST tests. However, when comparing the younger euthymic patients with the older ones, we did not observe any important differences, which supports our hypothesis that it might not be the age of the subjects studied that will determine the effect on the FAB or FAST tests, but most probably the time of the disease. We know that many of the youngest patients (≤ 40.5 years old) in our euthymic group have had the pathology for more than 10 to 15 years, while many older patients (≥ 40.5 years old) had recently started the disease; less than two or three years ago. After this discovery, we started planning a new study with a division of two groups of euthymic patients with early (less than 2 years) and late (more than 10 years) diagnoses of the disease, and we will reapply the above tests. We also intend to better clarify the issue of the impact of the number of crises of depression and mania on the evolution of the disease by collecting more data, even though it was not our initial intention. Thus, our partial results are supported by many authors in the literature that showed cognitive deficits, including EF, memory, and attention, and do not seem to be strictly a later effect of years of illness, because young people who had a recent manifestation of BD, had cognitive deficits that resemble that of adult patients, and these deficits can be observed even during euthymia [107];[78]; [108];[109]. Recently, in important research, [110] evaluated a sample of 51 euthymic bipolar patients, who were followed up for a mean period of 73 months. They suggested that a longitudinal trajectory of cognitive deficits in BD is relatively independent of the number of episodes or time

spent ill, and there were no differences between these patient groups in any clinical or neurocognitive variables at baseline. Also, **Pavuluri et al. [111]**, followed pediatric patients with BD for 3 years. They observed that all neuropsychological profiles remained impaired, especially EF and verbal memory even though the patients were treated and in remission. In a meta-analysis of pediatric patients with BD, it was concluded that the effect sizes of the tests in the different domains indicated greater deficits among the BD group, compared to the healthy controls, although they varied greatly in the effect size. i.e. verbal learning and memory ($Z = 4.65$, nine studies); executive function ($Z = 4.07$, nine studies); and attention ($Z = 3.81$, eight studies) [112]. However, our results differ from other researchers showing controversies in the literature about the cognitive impairment associated with BD. In a meta-analysis, **Samamé et al. [113]** described that bipolar patients' performance in 14 cognitive measures remained stable after a mean follow-up period of 4.62 years. When the meta-analysis was restricted to controlled studies, no patient-control differences were found regarding longitudinal cognitive outcomes. Also, **Cacilhas et al. [114]** found a significant correlation between age and functionality through the FAST test in BD patients. They demonstrated that BD was an important effect modifier on the natural age effects in general functioning, further characterizing BD as a chronic and impairing illness.

We must remember that this study was conducted with a clinical sample (or prevalence sample), which might tend to overestimate the morbidity, the cognitive deficits, and the functionality of patients with BD. We included in our sample patients with less than two years and more than ten years of length of illness and with very different numbers of previous affective episodes. We must also point out that, in our work, we use BD I / II patients in the same group. However, meta-analyses indicate that people with BD II also have cognitive deficits in the same way, but slightly less severe than those seen in BD I [115]; [116]. Possibly, the results of our tests would have been different if we had categorized our population into two groups. Due to the latter, patients with BD I may reflect greater severity of the disease symptoms, and therefore the effects of drugs such as mood stabilizers and antipsychotics, which are more commonly prescribed for BD I than II, and in larger doses, would produce iatrogenic effects in their EF, as noted by **Balanzá-Martínez et al. [117]**, and with greater impacts on verbal memory and processing speed as well. However, whether these discrepancies are partly related to the long-term treatment of these patients or not, is not yet fully understood. A study demonstrated that patients treated with antipsychotics had worse results in the Trail Making Test [118]. However, in another study with a

sample of 44 bipolar patients on monotherapy with lithium, it was found that changes in EF, especially in domains that required inhibitory control, were independently related to the severity of symptoms and the medication used [119]. Also, another longitudinal research with a sample of 15 euthymic patients treated with lithium monotherapy, were assessed for cognitive impairment twice over a 2-year follow-up. Repeated measures showed that the euthymic group was cognitively impaired in EF, which was the main long-term neuropsychological deficit of BD, though it did not worsen over 2 years. Furthermore, the results showed that the persistence of these cognitive deficits did not appear to be influenced by any clinical or pharmacological variable, remaining stable over time [102].

A possible alternative hypothesis of our findings is that the common cause of cognitive deficits and adverse clinical course is determined by some pathophysiological alteration (i.e. neurodevelopmental abnormalities) underlying different subgroups of patients with BD. This hypothesis is supported by the involvement of the prefrontal cortex and prefrontal-subcortical pathways, which regulate both mood state and cognitive functioning, and might predispose to a greater magnitude of cognitive deficits and frequency of episodes [120];[121]. In contrast, another subgroup of patients without such factor might have relatively preserved cognitive functioning and a lower number of affective episodes. [122];[123]; [124]; [125].

To better relate the meanings of these clinical and cognitive changes which reflected in the FAB test, we needed to initially discuss and relate the neuroanatomical and pathophysiological changes with the results found. There are several studies linking the impact of different psychiatric illnesses on brain functioning, and its architecture [126];[127];[128]. Research has shown that BD presents a cyclical and recurrent course. More recently, pathophysiological changes in the brain have been observed, raising the hypothesis that this is a progressive, chronic and disabling disease. The concept of neuroprogression appears to explain this phenomenon, but this concept is still surrounded by controversy [128];[129];[8];[9]. However, if there is an increase in the allostatic load, it produces a cumulative physiological dysregulation related to the dysfunction of the hypothalamic-pituitary-adrenal axis, altering immunity, thereby activating pro-inflammatory mechanisms with subsequent activation of oxidative stress states [130]. With this sequence of phenomena, an inflammatory environment is created, inducing a significant risk of cognitive decline [131];[132];[133];[134]. As previously reported, all these events involve a pathological

reorganization in the brain, and therefore, are associated with morphological modifications, such as the volume reduction in the cortex and white matter of the prefrontal cortex [135];[136];[137];[138];[139]. These prefrontal cortex alterations are possibly secondary to multiple episodes of mania and depression during their lives. In addition to these multiple episodes, the number of hospitalizations and disease duration in bipolar patients might cause changes in their neurocognitive performance, with an impact on their daily functionality and psychosocial aspects [4];[5];[6];[140]. These structural alterations in the prefrontal cortex, produce cognitive deficits associated with an inferior functional state, similar to what occurs to some neurological patients, indicating that some of the functional impairments frequently reported by BD patients, may be due to cognitive impairment, which may be a vulnerability factor for BD, and can present itself before the onset of the disease and worsen with the progression of the same [141].

The prefrontal cortex is a heterogeneous region that comprises several specialized sub-regions, in which EF represents only one functional category within the lobes [142]. This is a region that communicates with the entire brain, receiving and sending projections of all types. It integrates with the limbic system, reticular system, hypothalamus, and neurotransmitter systems [143], involving the amygdala, the dorsolateral prefrontal cortex, insula, and anterior cingulate areas [144];[145];[146];[147];[128];[139]. Through neuroimaging, had been possible the comprehension of the neural structure and function underlying cognitive processes and it was possible to differentiate the areas of the prefrontal cortex responsible for the different components of EF, with three main regions: the orbitofrontal, the ventromedial, and the dorsolateral region.

The orbitofrontal region, project into the caudate nucleus and is responsible for the inhibition capacity. An injury is characterized by personality change, including behavioral disinhibition and emotional lability. The ventromedial region begins in the anterior cingulate cortex and projects to the nucleus accumbens, mediating motivational behavior. An injury is associated with a decrease in motivation, causing apathy, indifference to pain, lack of motor and psychic initiative. The dorsolateral region project into the caudate nucleus. Usually, this region is associated with components of EF, namely verbal fluency, cognitive flexibility, planning, decision making, inhibitory control, working memory, reasoning, problem-solving and abstract thinking. An injury in this area, leads to the inability to maintain attention, persevering thoughts, impaired reasoning as well as deficits in mental

flexibility [148];[149];[150];[151]. The same authors observed that the neuropsychiatric manifestations are related to neurocircuitry defects. Impaired EF, impulsivity and apathy, are characteristics of frontal-subcortical circuit dysfunction, and neuropsychiatric disorders, like attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, schizophrenia, and therefore BD may result from impairment that have a direct or indirect impact on the integrity or functioning of these areas and projections.

Recently, several researchers have sought to relate the six domains present in the FAB test, with different neural networks, demonstrated in **Table 10**, [54];[152];[153];[154];[155];[156];[157]. In this study, the anatomical lesions were correlated with all the FAB subtests. Executive dysfunctions and impairment in working memory are related to lesions in the prefrontal dorsolateral cortex. Abulia and apathy are related to lesions of the ventromedial cortex, and disinhibition and mood disorders are related with the orbitofrontal cortex. When applied to the FAB subtest, the conceptualization was more related to dorsolateral. The results of the conflicting instructions, and go-no-go subtests, were related to the ventromedial and orbitofrontal cortex respectively. These results found in our work are

fascinating, because each different region of the prefrontal cortex showed an altered subtest. A large number of these symptoms described above are observed daily during the care of bipolar patients, mainly during manic and depressive phases. However, the bipolar patients in our study were more than six months in euthymia. Even so, the results showed us significant losses in all functionality domains, as well as in some cognitive domains found mainly in EF. Some cognitive impairments persist even after remission symptoms, and many studies have shown that they are neuropsychological related, at least in part, to the psychosocial difficulties of these patients [91];[88];[158]. On the contrary, there is little data in literature about the use of the FAB test in bipolar patients, and it is difficult to correlate this data with the anatomical lesions analyzed. Therefore, further studies using the FAB test are necessary, to better comprehend these results. It is important to note that changes of the connections between the involved structures are critical in the emotional dysregulation and cognitive functions in BD. Researchers observed that some abnormalities in some components of these neural systems are more apparent in adolescence, while other prefrontal regions appear to progress more in young adulthood, suggesting a neurological development model for this disorder [159];[160];[37];[138];[109].

Table 10: Prefrontal cortex regions, projections, behavioral mediation and injury, correlate to different domains assessed by the FAB test in Bipolar Patients and their respective level of significance.

PREFRONTAL CORTEX REGIONS	PROJECTIONS	BEHAVIORAL MEDIATION	INJURY	FAB TEST CORRELATION	p
Orbitofrontal	<i>Caudate Nucleus</i>	<i>Inhibition Capacity</i>	<i>Behavioral Disinhibition Emotional Liability</i>	Go-No Go Task (Inhibitory control) Prehension Behaviour (Environmental autonomy)	0.026* 0.202
Ventromedial	<i>Accumbens Nucleus</i>	<i>Motivational Behaviour</i>	<i>Apathy Abulia</i>	Conflicting Instruction (Sensitivity to interference)	0.013*

Dorsolateral	Caudate Nucleus	Executive Functions	Verbal Fluency Cognitive Flexibility Planning Decision Making Inhibitory Control Problem-Solving Abstract Thinking Working Memory	Similarities (Conceptualization)	0.041*
	Basal Ganglia			Lexical Fluency (Mental flexibility)	0.147
				Motor Series (Motor programming)	0.064
		Memory			

FAB = Frontal Assessment Battery. Analysis of FAB subtests scores by t-test (*t*) (F) for independent samples, **p* < 0.05. (See Table 10.)

Although BD is related to cognitive deficits, these deficits do not appear to be universal. It is estimated that about 30% of BD patients in remission will have levels of cognitive performance within the normal range [161];[162]. Also, longitudinal studies have shown that fluctuations in mood states do not seem to explain many of the cognitive deficits during euthymia [163]; [164]. Thus, it becomes imperative to define whether the cognitive impairment presented during euthymia, precedes the onset of the disease, that leads to the hypothesis of alterations in the neurological development, or whether it results from the negative impact of BD on cognition that corroborates the theory of neurodegenerative process (neuroprogression). Some researchers believe in the coexistence of the two hypotheses. From a neuropsychological point of view, longitudinal studies that last more than one year, are practically non-existent, which makes it challenging to confirm the cognitive impairment and determine whether it is stable or progressive [165];[166];[35];[167];[8];[9]. One of the longer longitudinal studies with bipolar patients was performed by Santos et al. [83] which assessed the performance of 80 euthymic outpatients, using a group of neuropsychological tests and demonstrated that cognitive deficits in BD were stable during a follow-up after five years, except in verbal memory, showing that the clinical course during the follow-up period did not influence the course of cognitive dysfunction. Another important study conducted by [104], which followed-up a group of euthymic bipolar patients by 6 years, and using to evaluate the functionality the FAST test, observed that among the clinical factors, only longer illness duration was significantly related to slow processing, whereas strong relationships were observed between impoverished cognition along time and poorer psychosocial functioning. Although cognitive deficits remained stable on average

throughout the follow-up, they had enduring negative effects on psychosocial adaptation of the patients. Thus, we can hypothesize that patients with greater cognitive impairment are less able to control their disease, and as a result, they suffer a worse course of the disease. However, the presence of subtle deficits in cognitive functions provide an indication that cognitive impairment may represent a trace of vulnerability factors in the development of BD that is present before the onset of the disease, but gets worse as the disease progresses. Thus, BD is characterized by remarkable heterogeneity regarding cognitive outcomes and probably different potential clinical predictors may be related to such outcomes, i.e., previous mixed episodes, current subclinical depressive symptoms, previous hospitalizations, and old age, and should therefore be the focus to a treatment [88];[35];[168];[169]; [167];[170];[171];[172]. Also, many other studies have shown that euthymic patients continue to have difficulties at work and in their studies, showing low performance or difficulty in maintaining them, although it is less evident [173];[115];[127];[174].

Finally, one of the main objectives of this article was to correlate whether the data on cognitive deficits observed in euthymic patients can help explain functional deficits. Therefore, we attempt to evaluate the clinical capability of the FAB test in bipolar patients. Studies have shown that the FAB test may have a good capability to discriminate several conditions in different clinical populations, although the evidence is still incipient and scarce in psychiatric disorders, and the results should be interpreted with caution. After performing the Spearman Correlation Coefficient Test, by comparing the FAST and FAB test scores in euthymic patients our group was able to observe a moderate negative correlation, $r_2 = -0.53$; $p < 0.001$. This result represents that 53% of the variation of the FAST test

(functionality) is linearly related to the FAB test (cognition and EF), with the remaining 47% of the variation resulting from other factors not considered (duration of illness, time of hospitalization, number of manic or depressive episodes, among others). These results are in accordance with the literature we studied. In a systematic review of 52 studies, cognitive deficits were strongly associated with poor functioning in BD, both in cross-sectional and longitudinal studies [175]. In a meta-analysis, **Depp et al.**, [127] also observed the same correlation between cognitive deficits and functional impairment. The effects did not appear to be modified either by the clinical status, or the age or design of the study. As already reported above, these cognitive deficits tend to become stable over time [113];[83]. However, a small subset of patients showed a decline over time in cognitive functions as demonstrated by **Mora et al.** [104], after following a group of patients for 6 years. The strength of the correlation between cognition and the functional outcome depends on the tests used. **Baune et al.** [175] noticed minor effects when using the Global Functioning Assessment (GAF) Test. In a meta-analysis, **Depp et al.** [127] observed an overall mean correlation of 0.27, $p < 0.001$, and all of these previous studies corroborate our results.

As stated previously, studies on BD patients have shown that the predictors of cognitive impairment functioning, assessed by FAST, were subclinical depressive symptoms, and previous mixed episodes were strongly associated. These results support the evidence that the significant morbidity and severe clinical course of BD lead to greater cognitive impairments with long-term consequences. Several researchers have demonstrated an apparent linear relationship between the increase in depressive symptoms and functional impairments, even during subsyndromal depressive conditions, which would increase the likelihood of depressive relapses. This is due to a stabilization meantime for bipolar depression, which is 24 weeks, while patients with mania need 11 weeks, and patients with mixed cycling episodes need 40 weeks [176];[177];[178];[179];[167];[170];[172]. **Rosa et al.** [24] concluded the same results, indicating that depressive symptoms are associated with a greater negative impact on psychosocial functioning than manic (hypo) symptoms. Other deficits in functioning seem to persist even during remission. These results showed the importance of treating depression and mania early, and the need to develop psychosocial interventions to improve functional results. The use of traditional psychopharmacology associated with psychoeducation has allowed the remission of the clinical symptoms to remain stable for more extended periods, which is an achievable

goal for many BD patients. However, it is no longer just about improve the patients or their remitting symptoms; but mostly improve their recovery. Unfortunately, studies showed that psychoeducation did not alter neurocognitive functioning on a neuropsychological test battery when compared with treatment as usual or cognitive behavioral therapy in altering dysfunctional negative beliefs [180];[181];[182];[183];[67]. Although our patients were participating in a psychoeducation group for more than two years, we observed similar results in our study, with many significant alterations in the cognitive and functional domains. Thus, the mood stability must come with the improvement of the processing speed, of the memory, and the EF, in addition to better psychosocial, interpersonal, and occupational functioning. These are fundamental objectives to be achieved.

V. CONCLUSION

As far as we know, this is one of the first studies that used the FAB test to assess the influence of various demographic and clinical variables, related to executive dysfunctions in BD. Although we adopted relatively strict inclusion criteria in our study, we recognize that our results should be evaluated with caution due to several limitations, which mainly derived from the administered neuropsychological tests, the sample size, and the cross-sectional design of the study. However, the limitations of the FAB and FAST tests, as well as the sample size, were partially resolved through the inclusion of a healthy control group, and the statistical evaluation regarding the sample sizes. Besides the above mentioned, there is also the clinical heterogeneity of the sample, which included patients with short- and long-term illnesses, who had different levels of education and age, which interfered in the analyzes. Another limitation was our cross-sectional design, where the data did not allow the analysis of the cause-and-effect relationship, and also studying many variables and their different areas of functioning. Regarding the FAST test, we did not control factors that could affect functional outcomes such as psychosocial interventions, familiar support, housing, and financial resources. The last weakness of our work is the lack of a deeper analysis regarding the impact of the treatments and medications used. As these patients have a chronic disease, they have had several previous treatments that may be related to current cognitive and functional deficits. This will be evaluated in future research that is already being planned. Thus, a larger sample can improve the performance of the FAB test, in addition to a better division into more clinically defined subgroups and a better control of some variables. Furthermore, our group started a new study with bipolar patients who had early and late-onset of the disease, and we are trying to assess

the functionality and cognitive impairment of these patient groups, continuing to include and controlling more variables.

However, the so-called euthymia in the BD does not mean full recovery of the patient, and this was very clear in our group during this study. Most of our bipolar patients participated in a psychoeducation program for more than 2 years, and all were outpatients with more than 6 months of euthymia. Therefore, we expected a better response to the FAST and FAB test scores compared to what was observed in other studies. However, the present study revealed that the data of our euthymic patients showed similar deficits in specific cognitive components, and these were associated with all domains of the FAST test, showing similar results with the literature.

Despite the clinical interest, there is a gap in terms of studies of the FAB test in bipolar patients, impairing the assessment as reliability and as validity that can correspond clinically. Although the FAB test shows some limitations, there is some evidence to suggest that several FAB test domains may have good predictions. In terms of clinical practice, early and differential diagnoses are crucial elements in determining the appropriate treatments and therapies. In this sense, the FAB subscores can offer useful information to increase the accuracy of the diagnosis, which can also be of considerable importance during advanced stages in which the progression of the disease intensifies executive dysfunctions. The total performance of the FAB test can be used as a marker of severe disease, rather than a single screening test. Furthermore, we can evaluate the effectiveness of neuropsychological rehabilitation programs in future studies, measuring the results and the qualitative analysis of their performance and also associate the impairments observed in cognitive functioning with possible brain dysfunctions. Following these strategies, it is necessary to promote functional recovery, which in many cases is not achieved through the available treatments today, which focus mainly on stabilizing mood episodes and preventing possible relapses. So far, there is no specific therapy or approaches to prevent the onset of this disorder or to treat it at the beginning of the disease. Many techniques have been developed to improve cognition in neuropsychiatric diseases. However, more recently, new approaches, such as functional remediation and dialectical behavior therapy (DBT), have been used. These techniques cover psychosocial aspects and regulations of emotions [184];[185];[186]. Functional remediation seeks to improve aspects related to work, functional and interpersonal skills, increasing autonomy, and reducing financial dependence. On the other hand, the core of DBT is to help people build four essential skills: mindfulness,

distress tolerance, interpersonal effectiveness, and emotional regulation. Recently these new approaches have been used to treat patients with BD [187];[188];[189]. Thus, through this research, our group aims to select patients for a future study about DBT, allowing them to develop new behaviors and skills. Thus, we aim to prevent and minimize the impact of any deficits found in their daily lives through cognitive training, and thus, promote their future reintegration into the community, improving their quality of life and reducing health expenses through the prevention of relapses.

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